REMARKS

Claims 1-18 are pending in the application. The claims have been amended to correct matters of form and/or clarity. Support for the amendment of claim 1 may be found in the present specification, for example, at page 15 line 12 to page 16, line 6 and Examples 1 to 3. Claim 19 has been cancelled. No new matter has been added by way of the above amendments.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-8 and 10-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Weiss etal. (US Patent 5,981,165). Applicants respectfully traverse.

Applicants respectfully submit that the "embryonic stem cells" disclosed in Weiss et al. are neural stem cells isolated from the brains of E14 (embryonic day 14) embryonic mice, (i.e., adult (somatic) stem cells), and such neural stem cells are clearly different from the ES cells (embryonic stem cells) as taught in the present invention, which are pluripotent cells established from blastocysts (E3.5 blastocysts).

In addition, there is no evidence that the cells isolated in Weiss et al. are neural stem cells (differentiation into neurons, astrocytes, or oligodendrocytes). Moreover, it is likely that the isolated cells are neural precursor cells committed to the neurons. The astrocyte conditioned medium (ACM) contains a neurotrophic factor for the neural precursor cells once committed to the neurons, and allows the neural precursor cells to differentiate into neural cells as long as the cells are alive.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Weiss fails to teach each and every element of the present invention because the differentiation of the cells obtained in Weiss et al. into neurons in the ACM is completely distinguishable from the differentiation of the ES cells or the undifferentiated neural stem cells in the ACM into neural stem cells and neural cells as taught in the present invention. Accordingly, the present invention cannot be anticipated by Weiss et al.

Applicants respectfully request reconsideration and withdrawal of the outstanding rejection.

Rejection Under 35 U.S.C. §103(a)

The Examiner rejected claims 1-3 and 1-12 under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (Nature Biotechnology, 19:1129-1133, 2001, IDS) in view of Flax et al., (Nature, 16:1033-1039, 1998). Applicants respectfully traverse.

Applicants respectfully submit that Zhang et al. describes a method in which colonies of ES cells are grown as embryoid bodies (EB) by a suspension culture, and the resulting cells are then subjected to adhesion cultures and addition of FGF-2, thereby producing neural precursor cells having a rosette structure. According to this method of Zhang et al., the neural cells are produced by selecting the neural precursor cells having a rosette structure according to their sensitivities to an enzyme treatment, growing the neural precursor cells with adult neural stem cells by a conventional neurosphere method, and subjecting the resulting proliferated cells to adhesion culture with a medium without addition of FGF-2. This method of Zhang et al. is a modification of a conventional method using EB; the method of selecting neural precursor cells is merely modified in that the sensitivity to an enzyme treatment is utilized.

In other words, the Zhang et al. method merely performs a procedure of selecting from other cells neural precursor cells that are differentiated from ES cells at a given frequency, not a method of directing the differentiation of the ES cells directly. Furthermore, according to the neurosphere method, not all of the neural precursor cells can be maintained in an undifferentiated state. In addition, the selected neural cells are a mixture of three kinds, i.e., neurons, astrocytes, and oligodendrocytes that appear at the same time.

On the other hand, the method of the present invention is intended to produce neural stem cells by directly differentiating the ES cells, to thereby positively direct the differentiation of the ES cells. In addition, according to the method of the present invention, the neural stem cells derived from the ES cells can be selectively differentiated into only neurons or astrocytes. It is clear from the present specification that the neural cells are directly differentiated from embryonic stem cells. See the present specification, for example, at page 15 line 12 to page 16, line 6 and Examples 1 to 3.

Therefore, Applicants submit that the present invention is neither taught nor suggested from Zhang et al. Flax does not cure the deficiencies of Zhang et al. Like Zhang et al., Flax teaches neural cells that are a mix of all neural lineages.

In accordance with *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007), in formulating a rejection under 35 USC 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

The Examiner bears the initial burden of presenting a *prima facie* case of obviousness. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of

obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336, quoted with approval in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007).

The Examiner alleges in the Office Action at page 5, the first full paragraph, that "*at the time the claimed invention was made, Flax et al. teach functional cryopreservable human neural stem cells can be propagated in culture in vitro*." However, the mere fact that this was known in the art at the time of the present invention does not establish why a person of ordinary skill in the art would have combined the prior art elements in the manner suggested by the Examiner. A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000). The present invention is not directed to mere "propagation" of cells. The Examiner has not provided an objective reason to combine the teachings of the references.

Thus, even if Zhang et al. were combined with Flax, it is clear that the present invention is not rendered obvious by the combined references. Accordingly, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection.

Rejection Under 35 U.S.C. §102(b) / 35 U.S.C. §103(a)

Claims 1-18 stand rejected under 35 U.S.C. §102(b) as anticipated by Zhang et al., or, in the alternative, under 35 U.S.C. §103(a) as obvious over Zhang et al. in view of Pataky et al., (Exp. Neurol. 163(2):357-372, 2000 (IDS)). Applicants respectfully traverse.

As discussed above in the context of the 35 U.S.C. §103 rejection, Zhang et al. fails to teach or suggest a method of directly differentiating the ES cells, as in the present invention. On this basis, Zhang et al. cannot properly anticipate the presently claimed invention.

Moreover, Applicants respectfully submit that Pataky et al. fail to cure the deficiencies of Zhang et al. Pataky et al. conclude that while FGF-2 and ACM show actions of promoting for survival of bulbospinal neurons, the ACM-promoted activity is due to a factor other than FGF-2. However, Applicants respectfully submit that the Examiner has mischaracterized the Pataky et al. disclosure by alleging that the ACM-promoted activity is due to FGF-2.

According to Pataky et al., in order to identify bulbospinal neurons, a crystal of DiI is contacted with the cervical spinal cord of ES chick embryo. Three days later on E8, the brain stems are subjected to dispersion culture, and the DiI-labeled neural cells are then identified as bulbospinal neurons, to find the effects of FGF-2 and ACM. The principle of labeling the neural cells with a fat-soluble fluorescent dye DiI is based on diffusion within a biomembrane, which is retrograde tracing in the spinally projecting axon.

In other words, cells capable of being labeled with DiI are only bulbospinal neurons of which the axon extends into the cervical spinal cord. More specifically, the effects of ACM are examined on DiI-labeled premature neural cells, which are already differentiated to extend neurites. Therefore, Pataky et al. clarify the promoting action for survival of ACM of the neurons themselves, so that Pataky et al. is completely irrelevant to the method of the present invention, which is differentiation of the ES cells and the ES cells-derived neural stem cells in the presence of ACM.

Accordingly, it is clear that the present invention is not rendered obvious by the combination of Zhang et al. and Pataky et al. Applicants respectfully request reconsideration and withdrawal of the outstanding rejection.

In view of the foregoing, Applicants believe the pending application is in condition for allowance. A Notice of Allowance is earnestly solicited.

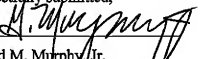
Conclusion

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Monique T. Cole, Reg. No. 60,154 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

Dated: December 20, 2007

Respectfully submitted,

By: 

Gerald M. Murphy, Jr.
Registration No.: 28,977
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant